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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/938,544	08/27/2001	Evan W. Steeg	1669.0070002	3690

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EXAMINER	
SAKELARIS, SALLY A	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 08/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/938,544	STEEG ET AL.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *4-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Priority

If applicant desires priority under 35 U.S.C. 120 based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

It is noted that applicants attempted to clarify their priority being claimed in the first line of the specification, it is suggested however that Applicants amend the first line of the specification to clarify the relationship between the present application and the parent and provisional application, for example: "The present application is a continuation of 09/726,427, filed 12/01/2000, which claims the benefit of priority under 119(e) to 60/168,625, filed 12/03/1999".

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code(Pg. 7, for example). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1 and 2 are rejected under 35 U.S.C. 102(a) as being anticipated by Golub et al.(Science 1999).

With respect to Claim 1: Golub et al. teach a method for diagnosing acute lymphoblastic leukemia (ALL), comprising(Pgs 531-537):

(a) measuring the levels of gene expression of leukotriene C4 synthase (LTC4S)(referenced web site in legend to Figure 3B was visited and "Ctrl F" was used to locate gene in the site's data set) gene and Zyxin(Figure 3B)in a biological sample taken from a patient suspected of having ALL(Pg. 531 Rt. Column); and

(b) comparing the levels of gene expression in said biological sample with a standard sample, wherein low levels of expression are indicative of a diagnosis of ALL(Figure 3B and pgs 531-536).

With respect to claim 2: Golub et al. teach a method for diagnosing ALL comprising:

(a) measuring the levels of gene expression of LYN V-yes-1 Yamaguchi sarcoma(referenced web site) viral related oncogene homolog, PPGB Protective fro beta-galactosidase, and Zyxin(Figure 3B)in a biological sample taken from a patient suspected of having ALL(Pg. 531 Rt. Column); and

(b) comparing the levels of gene expression in said biological sample with a standard sample, wherein low levels of expression are indicative of a diagnosis of ALL(Figure 3B and pgs 531-536).

Golub et al. is relied upon in the present specification as the "the pre-processed data"(Pg. 8) and therefore is seen as teaching the method as claimed. The specification rather teaches that "the patterns inherent in the system[of Golub et al.] are uncovered" by the present invention's application of various secondary methods such as the "coincidence detection" and "Matthews correlation" method. The Golub et al. reference teaches the up and down regulation of only the 50 genes listed in the figure 3B directly and by incorporation teaches the remaining genes' expression levels through the complete list of gene names, accession numbers, and raw expression values, on the MIT, Whitehead Institute's web site(see attached as a reference).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claim 3 is broadly drawn to a method for determining a prognosis of a patient with AML wherein high levels of GB DEF = homeodomain protein HoxA9 mRNA is indicative of a favorable prognosis. However, as will be further discussed, there is no support in the specification and prior art for the correlation of determining a patient's favorable prognosis and the over-expression of HoxA9 mRNA, only a correlation between HoxA9 mRNA's over-expression and a relatively poor prognosis has been taught. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001). The invention is a method for determining the prognosis of a patient with AML by applying the "coincidence detection" method as well as the "Matthews correlation" method to "pre-processed data"(Pg.8). The specification teaches that their application of these methods will cause "the patterns inherent in the system to be uncovered"(Pg.8). The practice of this invention requires knowledge that Hox9A mRNA over-expression is correlated to a favorable prognosis, ie as defined by Merriam Webster, "the prospect of recovery as anticipated from the usual course of disease or peculiarities of the case" of AML will be favorable. The practice of this invention requires

knowledge that the known oncogene, Hox9A, operates in an opposite manner than is currently known in the art, and specifically that another mechanism exists that causes the Hox9A gene's over-expression to be related to a favorable prognosis instead of its traditional marker of poor prognostic cases.

The unpredictability of the art and the state of the prior art

At the time the invention was made, the art taught "the single most highly correlated gene out of the 6817 genes (affymetrix array) was the homeobox gene HOXA9, which was over-expressed in patients with treatment failure(Golub et al. Science, 1999, Pg. 533). The Golub reference, on which the present invention relies further teaches that "HOXA9 over expression has been shown to transform myeloid cells in vitro and to cause leukemia in animal models" (Golub et al. Science, 1999, Pg. 533). The prior art provides no support for the ability of determining a prognosis of a patient with AML wherein high levels of GB DEF = homeodomain protein HoxA9 mRNA are indicative of a favorable prognosis. In addition, the post filing date art substantiates the prior art in its teaching that "AMLs with favorable cytogenetic features were associated with low overall HOX gene expression whereas poor prognostic cases had high levels"(Drabkin et al. Leukemia, 2002 Pg. 186). The post filing date art continues to teach that "our initial results suggest low HOX expression may be similar to good prognostic cytogenetics...In contrast, while patients with high HOX expression do less well overall"(Drabkin et al, Pg. 193). Lastly the reference refers back to the earlier relied upon piece of art in their teaching that "our results are consistent with the report of Golub et al using gene expression microarrays, who noted that HOXA9 was the single best predictor of outcome in patients with AML"(Drabkin et al., Pg 193).

Working Examples

The specification has no working examples of the method for determining the favorable prognosis of a patient with AML through a correlation made to an overepression of HoxA9 mRNA. While there is the expression data incorporated by reference to Gorub et al, no working examples exist to teach away from their contrary findings.

Guidance in the Specification.

The invention is a method for determining the prognosis of a patient with AML by applying the "coincidence detection" method as well as the "Matthews correlation" method to "pre-processed data"(Pg.8). The specification teaches that their application of these methods will cause "the patterns inherent in the system to be uncovered"(Pg.8). The practice of this invention requires knowledge that Hox9A mRNA over-expression is correlated to a favorable prognosis, ie as defined by Merriam Webster, "the prospect of recovery as anticipated from the usual course of disease or peculiarities of the case" of AML will be favorable. The practice of this invention requires knowledge that the known oncogene, Hox9A, operates in an opposite manner than is currently known in the art, and specifically that another mechanism exists that causes the Hox9A gene's over-expression to be related to a favorable prognosis instead of its traditional marker of poor prognostic cases. The specification provides tables of data and reiterates the results of Golub et al., but does not definitively identify that the HoxA9 gene is in fact predictive of a prognosis favorable or not for AML(Appendix A and C).

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Quantity of Experimentation

The level of skill in the relevant art is high, but the unpredictability with regard to the practice of the claimed invention is higher. To practice the invention as claimed one would have to practice much experimentation to find an alternate mechanism by which HOXA9 acts in order for its over-expression to result in a favorable prognosis instead of that which is known in the art as its action as an oncogene. An extremely large quantity of experimentation would be necessary to practice the claimed invention, void of any such similar teachings in the specification as filed and the art.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the ability to correlate the overexpression of a well known oncogene with a favorable prognosis depends upon numerous known and unknown parameters such as the mechanism and structure responsible for HoxA9's putative duality in its abilities of prognosticating AML, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems in the use of the correlating HoxA9's overexpression with a favorable prognosis for an AML patient as broadly claimed. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (703) 306-0284. The examiner can normally be reached on Monday-Thursday from 7:30AM-5:00PM and Friday from 1:00PM-5:00PM.

If attempts to reach the examiner are unsuccessful, the primary examiner in charge of the prosecution of this case, Jeffrey Fredman, can be reached at (703)308-6568. If attempts to reach the examiners are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)308-1119. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (703)605-1237.

Sally Sakelaris

8/14/2003

JEFFREY FREDMAN
PRIMARY EXAMINER